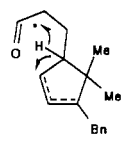

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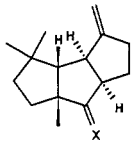
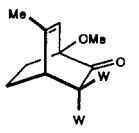


14 X=H$_2$
15 X=O



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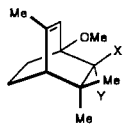
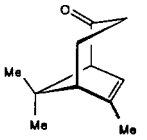


18 X=H,Y=OH
19 X=OH,Y=H



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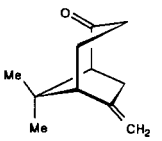

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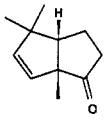

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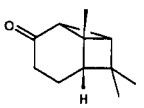

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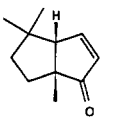

24

bicyclo[3.2.1]oct-6-en-2-ones (8).

The latter transformation has been applied to a total synthesis of (±)-$\Delta^{9(12)}$-capnellene (14).[7,8] Treatment of **16** with *t*-BuOK, MeI in THF followed by reduction with $LiAlH_4$ gave a ca. 1:1 mixture of the *exo*- and *endo*-alcohols (**18** and **19**, respectively) in 80% overall yield. Pinacol-type rearrangement[9] of **18** proceeded by heating under reflux with TsOH (1 equiv) in benzene for 2 h to give a 5:1 mixture of the desired ketone **20** and the exocyclic olefin **21** in 95% yield. The isomeric alcohol **19** was recycled to **17** by Collins oxidation in 97% yield, because of inertness to the conditions for the rearrangement.

A photochemical reaction of **20** by irradiation in acetone gave the [5–5] fused ring ketone **22** and the [1,2]-acyl migration product **23** in 51% and 13% yields, respectively, when the reaction was stopped at 81% of conversion. This outcome indicates that, in the case of runs 8 and 10, steric crowding within the substrates due to the substituents is a factor that diminishes formation of the [1,2]-acyl migration products.

Catalytic hydrogenation of **22** followed by treatment with *t*-BuOK and $ClCOOCH_2CH{=}CH_2$, and then with $Pd(OCOMe)_2$ in MeCN[10] gave the ketone **24**, in 52% overall yield, from which (±)-**14** had already been derived.[8h] An alternative route to **14** is the sequential treatment of **24** with (1) the copper reagent, $LiCu(C(=CH_2)CH_2CH_2OSiMe_2$-*t*-$Bu)_2$,[11] (2) acetic acid in aqueous THF, (3) TsCl and NEt_3 in CH_2Cl_2, (4) $LiN(SiMe_3)_2$ in THF (to give the triquinane **15** in 86% overall yield from **24**), (5) $LiAlH_4$ in ether, (6) NaH, imidazole, CS_2, and then MeI, and (7) $(n\text{-}Bu)_3SnH$ and AIBN in toluene (to give the hydrocarbon **14** in 26% overall yield from **15**). The spectral data of **14**, thus obtained, was identical with those of (±)-$\Delta^{9(12)}$-capnellene.[8e]

Acknowledgment. We thank Professor H. Shirahama of Hokkaido University for copies of the spectra of synthetic (±)-$\Delta^{9(12)}$-capnellene.

Supplementary Material Available: Experimental procedure for the preparation of **8a** and spectral properties for **7a,d,e**, **8a–e**, **9a–c**, **10**, **12**, **15**, **17–20**, **22**, and **23** (7 pages). Ordering information is given on any current masthead page.

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Enantioselective Construction of a Quaternary Asymmetric Carbon Center: A Versatile Synthesis of α-Alkyl α-Amino Acids

Masataka Ihara, Masanobu Takahashi, Hiroko Niitsuma, Nobuaki Taniguchi, Ken Yasui, and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Received August 28, 1989

Summary: The enantioselective construction of a quaternary asymmetric carbon center was developed through reaction of the dianions derived from the chiral half esters of monosubstituted malonic acids with 2 molar equiv of LDA and alkyl halides. Alkylation in the reverse sequence preferentially gave the same diastereoisomer. The alkylated half esters were transformed into α-alkyl α-amino acids.

Sir: The enantioselective transformation of prochiral malonic acids into unsymmetrical molecules would be one of the preferred methods for providing versatile chiral building blocks[1] for the synthesis of optically and biologically active compounds. While this type of asymmetric synthesis is common in enzymatic conversions,[2] examples of its use in chemical transformation are rare.[3] Previously

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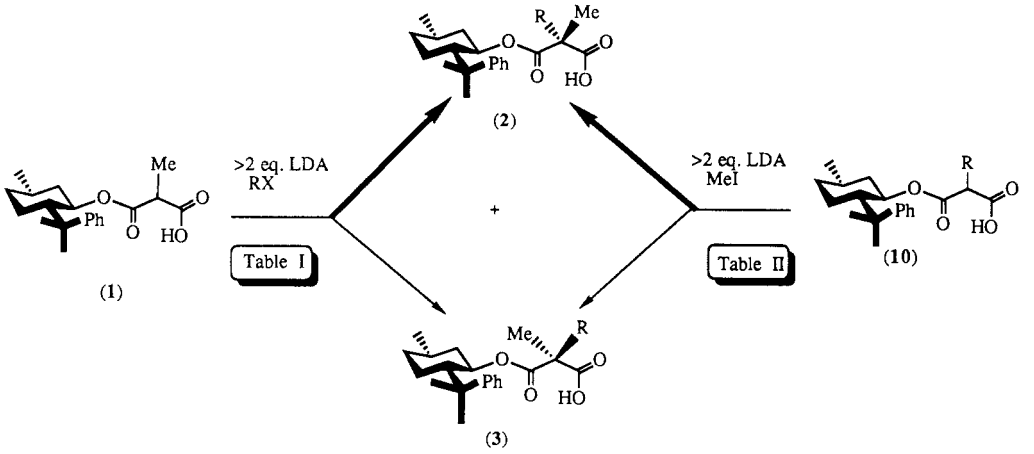
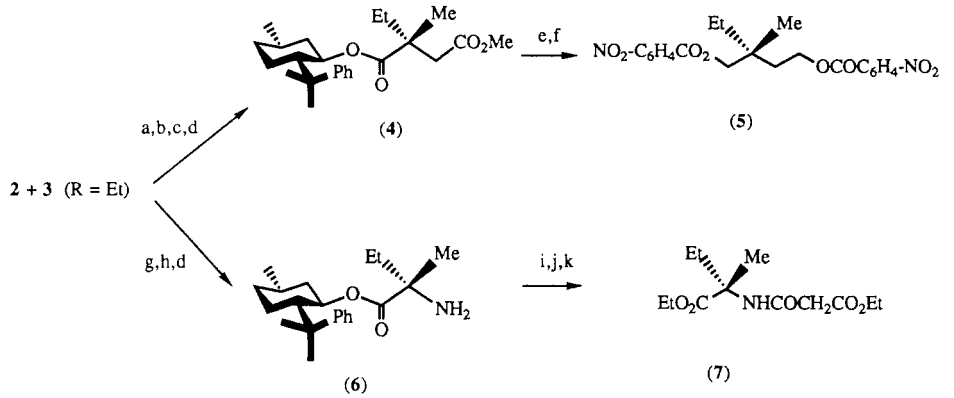
Scheme I



Scheme II[a]



[a] Reagents: (a) $(COCl)_2$; (b) CH_2N_2; (c) AgOCOPh, MeOH; (d) HPLC; (e) LAH; (e) LAH; (f) *p*-$NO_2PhCOCl$, pyridine, DMAP; (g) $(PhO)_2PON_3$, Et_3N; $PhCH_2OH$; (h) Pd–C, cyclohexene; (i) KOH, 18-crown-6; (j) HCl–EtOH; (k) EtO_2CCH_2COCl, DMAP.

we reported the asymmetric preparation of chiral propane-1,3-diols from monosubstituted malonic acids through the use of chiral alcohols, and the possibility of achieving high degrees of enantioselection induced by second-order asymmetric transformations.[4] Our attention recently focused on the enantioselective alkylation of chiral half esters of monoalkyl malonic acids in order to create a quaternary asymmetric center. The investigation led us to discover a novel and enantioselective construction of a quaternary asymmetric center in high optical purity and an efficient route to α-alkyl α-amino acids, the subject of much recent attention in the biological community.[5]

Table I. Alkylation of Half Ester 1

entry	RX	reaction temp, °C	reaction time, h	yield, %	ratio of 2 and 3
1	EtI	−25	10	83	4:1
2	^nPrI	−25	10	72	4:1
3	$CH_2{=}CHCH_2I$	−78	12	77	7:1
4	$CH_2{=}CMeCH_2I$	−78	12	91	6:1
5	$PhCH_2Br$	−25	14	72	12:1
6	$2\text{-}NO_2PhCH_2Br$	−25	14	94	10:1
7	$3,4\text{-}(MeO)_2PhCH_2Br$	−25	14	75	12:1
8	$4\text{-}MeOPhCH_2Br$	−25	14	71	12:1
9	$2\text{-}MeOPhCH_2Br$	−25	14	73	16:1

Dianions formed from chiral half esters were expected to act as good nucleophiles in effecting enantioselective substitution with alkyl halides.[6] Alkylation of the half esters was tested using various bases, and it was found that reaction proceeded smoothly with more than 2 equiv of LDA or LHMDS in THF. Poor selectivity, observed on addition of HMPA,[7] indicated the potential for intramolecular chelation. The results of the alkylation reactions of 1,[4] prepared from methylmalonic acid and (−)-8-phenylmenthol,[8] are shown in Table I.

Ratios of the two diastereoisomers were determined by 500-MHz ^1H NMR spectroscopy of the products and

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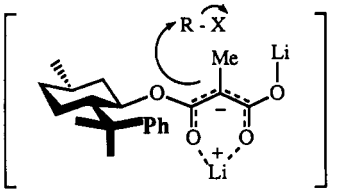


(A)

Figure 1. Transition state of alkylation of phenylmenthyl hydrogen methylmalonate 1.

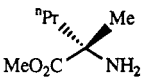
HPLC analysis following conversion to methyl ester using CH_2N_2. Absolute configurations at the 2-position of the major components were determined by comparisons with known compounds. Following Arndt–Eistert reaction of the product (entry 1) (51% yield) and HPLC separation, the major product **4** was converted into the (−)-(*R*)-di-*p*-nitrobenzoate **5**: mp 154 °C; $[\alpha]^{24}_D$ −1.93° ($CHCl_3$) [lit.[9] mp 154 °C; $[\alpha]^{20}_D$ −1.8° ($CHCl_3$) in 78% overall yield. The assignment was confirmed by transformation into the α-methyl α-amino acid **7**. Curtius type rearrangement[10] (77% yield), followed by hydrogenolysis (82% yield) and HPLC purification, gave the amino ester **6**, which was hydrolyzed using KOH and 18-crown-6 in hot toluene. The resulting amino acid was converted into the (+)-(*S*)-amide **7**, $[\alpha]^{20}_D$ +5.3° (benzene) [lit.[11] $[\alpha]^{20}_D$ +5.0° (benzene)], in 71% overall yield from **6** (Scheme II).

The major component of entry 2 was identical with the major one of the hydrogenated products of entry 3, and its stereochemistry was determined by similar conversion to the (+)-(*S*)-amino ester **8**, $[\alpha]^{28}_D$ +13.4° (EtOH) [lit.[12] (*R*)-form: $[\alpha]_D$ −13.0° (EtOH)]. The major isomer of entry 5 was similarly transformed to the (+)-(*S*)-acetamide **9**,

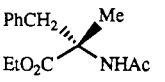
Table II. Methylation of Half Esters 10

entry	R	reaction temp, °C	reaction time, h	yield, %	ratio of 2 and 3
1	Et	−78	3	80	5:1
2	^{n}Pr	−78	3	63	5:1
3	$PhCH_2$	−78	5	61	15:1

$[\alpha]^{27}_D$ +49.2° ($CHCl_3$) [lit.[13] (*R*)-form: $[\alpha]_D$ −47.8° ($CHCl_3$)]. It is clear that the major products possess *R*



(8)



(9)

configurations at the 2-position. The actual *E*/*Z* distribution and conformations of the dianions are not known. The diastereofacial selectivity noted above could be attributed to easier access to the alkyl halides from the less hindered side of the transition-state geometry (A) depicted in Figure 1. In expectation of the preferential formation of the other isomers **3**, half esters **10**[4,14] were methylated (Scheme I), but the same isomers **2** were produced as the major products and in similar selectivities (Table II). Formation of the same diastereomers is not a serious drawback because chemoselective transformation of the major half ester would provide both enantiomers of various chiral building blocks. Further work will be required in order to clarify the mechanism of these suprising results.

In summary, a new methodology for the enantioselective construction of a quaternary asymmetric carbon and an efficient approach to α-alkyl α-amino acids were developed.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas, 01607002, from the Ministry of Education, Science and Culture of Japan.

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(14) The half ester **10** (R = CH_2Ph) was prepared in 72% yield by reaction of (1*R*,3*R*,4*S*)-8-phenyl-*p*-methan-3-yl hydrogen malonate and benzyl bromide in the presence of 2 equiv of LDA at −78 °C.

Complete Control of the Rearrangement Modes of Enolates of α-Allyloxy Ketones: Reversal from the [3,3]-Claisen to the [2,3]-Wittig Pathway by the Use of the Metalated *N*,*N*-Dimethylhydrazones

Juan I. Luengo† and Masato Koreeda*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

Received August 31, 1989

Summary: It has been shown that the predilection for the [3,3]-Claisen rearrangement pathway of enolates of α-allyloxy ketones is cleanly overridden by the [2,3]-Wittig rearrangement route with the use of carbanions of their corresponding *N*,*N*-dimethylhydrazones. Since the formation of these hydrazones as well as hydrolysis of the rearranged α-hydroxyhydrazones can be readily achieved, this approach allows a [2,3]-Wittig rearrangement pathway to take place in high yields starting from the α-allyloxy ketones.

Sir: Enolates of α-allyloxy ketones **1** (X = O) have recently been shown to undergo facile [3,3]-anionic oxy-Claisen rearrangement giving rise to α-hydroxy ketones **2** through a novel 1,2-carbonyl transposition.[1] In connection with another synthetic project in these laboratories, we required

†Present address: Department of Medicinal Chemistry, Smith Kline & French Laboratories, 709 Swedeland Road, Swedeland, PA 19479.

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